Reference Materials for Electron Microscopy of Particulate Drug Delivery Systems

Therapeutic drugs for parenteral delivery are now being "packaged" in the form of engineered particle drug delivery systems (DDSs). As DDS technology develops within the R&D and manufacturing communities, new demands will be placed on nano- and micro-scale methods to accurately characterize these systems chemically, including high-resolution electron microscopy. Concurrent with these demands will be demands for relevant reference materials to help qualify these methods at the size scale of the DDSs.

J.M. Conny (Div. 837)

Particulate drug delivery systems (DDSs) have a benign excipient framework that retains the drug within the framework until the particle reaches the drug's target at the optimal time. A variety of organic excipient materials are in use as approved DDSs or in various stages of R&D. These include liposomes and other lipids structured as micelles, conventional polymers such as polyethylene glycol and poly(lactic acid-co-glycolic acid), and more exotic polymers such as dendrimers. In addition to organic excipients, ceramic nano-particles are under study as intravenous DDSs.

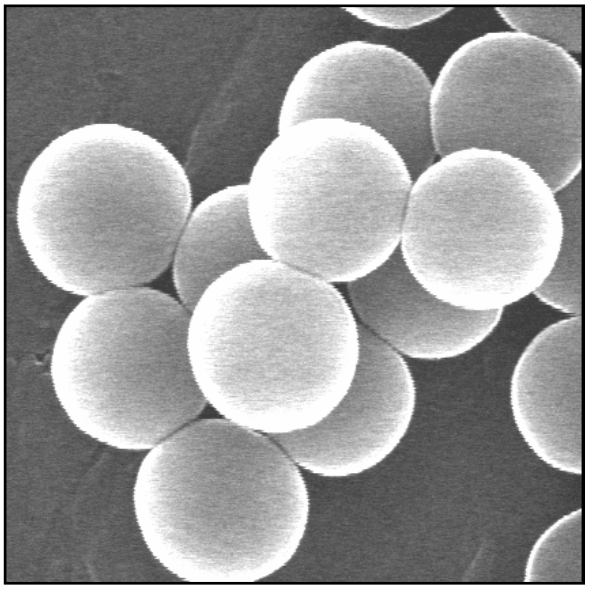
Of major concern is the potency of the drug associated with the delivery system. With the variety of excipients comes a range of drug-carrying capacities. A drug with low potency must be matched with a high-capacity excipient, and visa versa. Therefore, it is necessary to know the distribution of the number of drug molecules associated with the DDS and the spatial relationship of the drug molecules and excipient. Electron-beam methods such as TEM and SEM are useful tools for determining spatial relationship. Reference materials would help assess the accuracy the methods.

Silica DDSs offer advantages as first-case materials to study for two reasons. First, they are relevant materials because silica-based particles are, in fact, being developed as DDSs. Second, chemical characterization methods in electron microscopy such as X-ray microanalysis and electron energy loss spectroscopy should well distinguish the excipient Si atoms from atoms of the drug molecule.

NIST researchers use electron-beam microscopic techniques to understand the critical aspects of DDSs, such as the distribution of drug molecules in the system, and the spatial relationship of the drug within the excipient framework.

Accomplishments and Future Plans

- The first material studied in this effort is a silica sol encapsulating insulin. Sol-gel chemistry offers ideal routes to generating uniformly-sized particles at low temperatures through the selective control of organo-silicate reagents and pH. Emulsification methods allow the silica particle to "capture" the drug compound as the silica particle forms.
- In addition to silica-based systems, DDS reference materials with organic excipients are planned.



Field emission SEM image of 300 nm to 400 nm diameter silica particles.